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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

24197 7590 12/12/2006

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14,48 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,48 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was transferred to Examiner Quang Nguyen, Ph.D. in GAU 1633.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/10/06 has been entered.

Claims 9, 11-12, 14, 48 and 51 are pending in the present application, and they are examined on the merits herein with the previously elected species of diabetic lower limb ischemic disease.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

In claim 9 and its dependent claims, it is unclear what is encompassed by the term "few weeks". This is because it is unclear what are the lower and/or upper limits of

the limitation "few weeks". Would a period of 10 weeks or 13 weeks still be considered to be a few weeks? It is also noted that to some 20 weeks still being considered to be a few weeks. Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. (EP 0 847757 A1; IDS) in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a new ground of rejection.***

Morishita et al teaches a medicament comprising a membrane fusion liposome fused to Sendai virus containing a hepatocyte growth factor (HGF) gene, and a method for treating arterial disorders using the same medicament (col. 2, lines 4-19; col. 6, lines 12-33). Morishita et al further teaches that the HGF gene can also be incorporated into an appropriate vector, including a viral vector such as retrovirus, adenovirus, adeno-related virus and others (col. 6, lines 34-47). Morishita et al further discloses that the medicament can be administered through any route appropriate for diseases to be treated or target organs, including subcutaneously, intraarterially, intramuscularly (col. 7, lines 11-19); and that arterial diseases include insufficiency of peripheral circulation, arteriosclerosis, myocardial infarction, peripheral angiostenosis and others since HGF promotes the proliferation of vascular endothelial cells (col. 5, lines 12-34). Morishita et al further teaches that the content of the HGF gene in the medicament may be appropriately varied depending upon diseases to be treated, target organs, patient's age or body weights, etc. However, it is appropriate to administer a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, and that the dose may be divided into several days or a few months (col. 7, line 55 continues to line 3 of col. 8). This dosage teaching encompasses the ambiguous limitation "at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks".

Morishita et al does not specifically teach a method for treating diabetic lower limb ischemic disease in a subject using a medicament comprising a hepatocyte growth factor (HGF) gene.

At about the effective filing date of the present application (10/29/1999), the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis oblitrans mainly caused by diabetes mellitus and resulting in limb necrosis or gangrene by vascular occlusion. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Morisita et al. by also using a medicament comprising a HGF gene at a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, in the time frame taught to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Morishita et al. and the Japan Financial News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

It is also well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicant's arguments related in part to the above rejection in the Amendment filed on 10/10/06 (pages 5-7) have been fully considered along with the Declaration under 37 CFR 1.132 of Dr. Morishita filed 7/21/06, but they are respectfully not found to

be persuasive and insufficient to overcome the rejection of claims 9, 11-12, 14, 48 and 51 based upon Morishita et al. (EP 0 847757 A1; IDS) and the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) under 35 U.S.C. 103(a) as set forth above for the reasons discussed below.

1. Applicant argues that one skilled in the art would not have expected that the effect of HGF gene to be maintained even after a few days or weeks after its administration because the half-life of HGF is as short as about 10 minutes. Applicants further argue that the administration of HGF gene once every few weeks is therapeutic for subjects having diabetic ischemic disease, and that such infrequent administration would be therapeutic was not expected due to the short half life of HGF; and therefore this unexpected superior result rebuts any allegation that the cited references establish a prima facie case of obviousness.

Please note that in a gene therapy method, the effect of HGF gene would be expected to last at least several days or weeks or even months. This is because unlike protein therapy, transfected cells in the muscle of an ischemic site would be expected to continue to express exogenous nucleic acid encoding HGF and producing exogenous HGF for several weeks or even months, and the generated exogenous HGF continues to exert its effect. For example, Stratford-Perricaudet et al (J. Clin. Invest. 90:626-630, 1992; IDS) already demonstrated a long-term *in vivo* gene transfer throughout mouse skeletal and cardiac muscles using a recombinant adenoviral vector, showing the expression of a transgene can still be detected and sustained in muscle tissues after 10-12 month post-injection(see at least the abstract; and page 627, col. 2, first full

paragraph). Denham et al (J. Gastrointest. Surg. 2:95-101, 1998; IDS) and Denham et al. (Annals of Surgery 227:812-820, 1998; IDS) also demonstrated that cationic liposome-mediated gene transfer into pancreas resulted in tissue expression of the reporter gene or IL-10, respectively, for up to 2 weeks with no induction of pancreatic inflammation (see at least the abstracts). Therefore the infrequent administration of a recombinant vector expressing a gene of interest, such as HGF gene, to achieve a therapeutic effect is not totally unexpected as asserted by Applicants.

2. With respect to the broad dosage ranges cover those for various arterial diseases taught in the Morisita et al. reference, Applicants argue that a significant amount of experimentation was undertaken to determine the dose of HGF gene that would provide the desired therapeutic effects for treating diabetic ischemic diseases as claimed. The particular dosage or narrower range of doses was not obvious. Additionally, Applicants argue that it is known that angiogenesis hardly occurs and prognosis is unfavorable in diabetic ischemic diseases as evidenced by the previously submitted article of Melliere et al. (Eur. J. Vasc. Endovasc. Surg. 17:438-41, 1999). Accordingly, it would not be routine for one skilled in the art to determine the HGF gene dosage for diabetic ischemic diseases.

Morishita et al already taught that the content of the HGF gene in the medicament may be appropriately varied depending upon diseases to be treated, target organs, patient's age or body weights, etc. However, it is appropriate to administer a dose of 0.0001 mg to 100 mg, preferably 0.001 mg to 10 mg, and that the dose may be

divided into several days or a few months (col. 7, line 55 continues to line 3 of col. 8). This dosage teaching encompasses the ambiguous limitation "at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks". Alternatively, it is routine and it does not require any undue experimentation for an ordinary skilled artisan to determine the dosage used in the method as claimed, particularly in light of the state of the prior art of record. With respect to the cited Melliere et al. article, there is nothing in the reference indicates or even suggests that diabetic patients would not responsive to any angiogenic factor, let alone to HGF which is already recognized to have more potent angiogenesis activity and less side effects than VEGF, and suitable for treating patients with arteriosclerosis obliterans caused mainly by diabetes mellitus according to the Japan Financial News Paper dated 12/14/1998.

Accordingly, claims 9, 11-12, 14, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. (EP 0 847757 A1; IDS) in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS) for the reasons set forth above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9, 11, 14 and 48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-4 of U.S. Patent No. 6,989,374 B1 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a new ground of rejection.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks, thereby treating the diabetic ischemic disease.

Claims 1 and 3-4 of U.S. Patent No. 6,989,374 B1 are drawn to a method for treating a cardiac muscle disorder comprising administering a therapeutically effective amount of a nucleic acid molecule encoding HGF directly to a part of an affected abdominal lateral cardiac muscle or directly into an abdominal lateral cardiac muscle of a mammal using echocardiographic guidance without thoracotomy, wherein the nucleic

acid molecule is encapsulated in a Sendai virus-liposome and expresses an HGF protein that reduces fibrosis and/or promoting angiogenesis of the cardiac muscle.

The claims of the present application differ from the claims of the U.S. Patent No. 6,989,374 B1 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction. It is also noted that in the issued U.S. Patent No. 6,989,374 B1, the term "administering" includes once every few weeks; and the "effective amount" includes a range from about 10 to about 400 ug of HGF gene (col. 6, lines 58-62).

At the effective filing date of the present application, the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis oblitrans mainly caused by diabetes mellitus. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF and is therefore expected to be applied to myocardial infarction (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to apply the method of the U.S. Patent No. 6,989,374 B1 to a mammal or a subject having diabetes mellitus, particularly for treating myocardial infarction, in light of the disclosure of the Japan Financial News Paper dated 12/14/1998.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that gene therapy using a gene

encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars in a patient having diabetes mellitus. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF, and is therefore expected to be applied to myocardial infarction.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of U.S. Patent No. 6,989,374 B1 and the Japan Financial News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claims 9, 11-12, 14, 48 and 51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,248,722 (Cited previously) in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a new ground of rejection.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks, thereby treating the diabetic ischemic disease.

Claims 1-4 of U.S. Patent No. 6,248,722 are drawn to a method for treating a disease (including an arterial disease) in a subject for which HGF is effective, comprising administering intramuscularly to the subject an expression vector containing a HGF gene in a therapeutically effective amount.

The claims of the present application differ from the claims of the U.S. Patent No. 6,248,722 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction. It is also noted that in the issued U.S. Patent No. 6,248,722, the term "administering" includes administering a dose of 0.001 mg to 10 mg of HGF gene into several days or a few months (col. 6, lines 48-54). This dosage teaching encompasses the ambiguous limitation "at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks".

At about the effective filing date of the present application (10/29/1999), the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis oblitrans mainly caused by diabetes mellitus and resulting in limb necrosis or gangrene by vascular occlusion. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of U.S. Patent No. 6,248,722 by also using a medicament comprising a

HGF gene at a dose 0.001 mg to 10 mg, in the time frame taught to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of U.S. Patent No. 6,248,722 and the Japan Financial News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claims 9, 11-12, 14, 48 and 51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-11

of copending Application No. 10/615,262 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a new ground of rejection.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks, thereby treating the diabetic ischemic disease.

Claims 7-11 of copending Application No. 10/615,262 are drawn to a method for treating insufficiency of peripheral circulation or peripheral angiostenosis in a subject for which HGF is effective, comprising administering intramuscularly at the affected site a therapeutically effective amount of an expression vector containing a constitutive promoter operably linked to a HGF coding sequence.

The claims of the present application differ from the claims of the copending Application No. 10/615,262 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction. It is also noted that in the issued U.S. Patent No. 6,248,722, the term "administering" includes administering a dose of 0.001 mg to 10 mg of HGF gene into several days or a few months (page 15, lines 13-19). This dosage teaching encompasses the ambiguous limitation "at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks".

At the effective filing date of the present application, the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene

encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis oblitrans mainly caused by diabetes mellitus. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF and is therefore expected to be applied to myocardial infarction (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of copending Application No. 10/615,262 by also using a medicament comprising a HGF gene at a dose 0.001 mg to 10 mg, in the time frame taught to treat patients having arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion (e.g., intramuscular injection to a muscle around the affected limb of patients) in light of the disclosure of the Japan Financial News Paper dated 12/14/1998.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that arteriosclerosis obliterans mainly caused by diabetes mellitus and resulting in limb necrosis by vascular occlusion, and that gene therapy using a gene encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars and to avoid amputation of the limb. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of copending Application No. 10/615,262 and the Japan Financial

News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

Claims 9, 11, 14 and 48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-11 of copending Application No. 10/615,292 in view of the Japan Financial News Paper dated 12/14/1998 (English translation; IDS). ***This is a new ground of rejection.***

The instant claims are directed to a method for the treatment of diabetic ischemic disease in a subject, comprising administering a therapeutically effective amount of a hepatocyte growth factor gene to the muscle of an ischemic site, wherein at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks, thereby treating the diabetic ischemic disease.

Claims 7-11 of copending Application No. 10/615,292 are drawn to a method for treating myocardial infarction in a subject for which HGF is effective, comprising administering by direct intracoronary injection into heart muscle of a subject a therapeutically effective amount of an expression vector containing a constitutive promoter operably linked to a HGF coding sequence.

The claims of the present application differ from the claims of the copending Application No. 10/615,292 in reciting specifically a method for the treatment of diabetic ischemic disease, including diabetic ischemic myocardial infarction. It is also noted that in the copending Application No. 10/615,292, the term "administering" includes administering a dose of 0.001 mg to 10 mg of HGF gene into several days or a few months (paragraph 39 on page 11). This dosage teaching encompasses the ambiguous limitation "at least 50 ug of the hepatocyte growth factor gene is administered to the subject once every few weeks".

At the effective filing date of the present application, the Japan Financial News Paper dated 12/14/1998 already reported a proposed gene therapy using a gene encoding HGF having angiogenesis activity to be injected to a muscle around the affected part of patients having arteriosclerosis oblitrans mainly caused by diabetes mellitus. The paper further teaches that a gene therapy trial has already been conducted by Tuft University using a gene encoding VEGF; and that HGF has a more potent angiogenesis activity and less side effects than VEGF and is therefore expected to be applied to myocardial infarction (see the entire article).

Accordingly, it would have been obvious for an ordinary skilled artisan to apply the method of the copending Application No. 10/615,292 to a mammal or a subject having diabetes mellitus, particularly for treating myocardial infarction, in light of the disclosure of the Japan Financial News Paper dated 12/14/1998.

An ordinary skilled artisan would have been motivated to carry out the above modification because the paper clearly teaches that gene therapy using a gene

encoding HGF having angiogenesis activity can stimulate the regeneration of new vasculars in a patient having diabetes mellitus. Furthermore, HGF is also noted to have more potent angiogenesis activity and less side effects than VEGF, and is therefore expected to be applied to myocardial infarction.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of copending Application No. 10/615,292 and the Japan Financial News Paper dated 12/14/1998, coupled with a high level of skill for an ordinary skilled artisan in the therapeutic angiogenesis art at the effective filing date of the present application (see the cited art of record).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

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